Remarks

Claims 41-50 are pending in this application. Claim 41 is amended to remove the recitation of the term "racemic." Claim 51 is cancelled. Applicants reserve their right to pursue the subject matter recited by it in one or more divisional, continuation, and/or continuation-in-part applications.

Applicants respectfully submit that all of the pending claims are allowable for at least the following reasons.

A. The Rejection Under 35 U.S.C. § 103 Should Be Withdrawn

On pages 4-6 of the Office Action, claims 41-51 are rejected as allegedly obvious over WO 94/00047 by Young, or WO 94/00114 by Young (collectively referred to herein as "Young") in view of Luscombe *et al.*, *Neuropharmacology*, 28(2): 129-134 (1989) ("Luscombe"). In particular, the Examiner alleges that the claims are obvious based on the assertion that: 1) Young "teaches the importance of stereochemical purity in the field of pharmaceuticals where chirality is demonstrated"; and 2) Luscombe "teaches ... didesmethylsibutramine ... to be considerably more active than sibutramine." (Office Action, pages 4-6). Applicants respectfully traverse this rejection.

The U.S. Supreme Court has recently addressed the test for obviousness under 35 U.S.C. § 103. (*KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007)). In *KSR,* the Supreme Court rejected the Federal Circuit's *rigid application* of the "teaching, suggestion, motivation" test ("the TSM test") in determining obviousness in the particular case in question. (*Id.*, at 1739) (emphasis added). According to the Supreme Court, the correct standard to apply is set forth in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). (*See KSR*, 127 S.Ct. 1727, 1729). However, the *KSR* decision indicated that while the TSM test is not the sole method for determining obviousness, it may still be a factor. (*Id.*, at 1741 ("[w]hen it first established [the TSM test], the Court...captured a helpful insight.")). In fact, the Deputy Commissioner of Patents circulated a memorandum ("USPTO Memorandum," dated May 3, 2007) to the Technology Center Directors pointing out that the TSM test was not completely abolished in *KSR*.[1] Be that as it may,

[1] Therefore, Applicants respectfully reiterate all of the arguments made based on the TSM test presented in their previous responses, all of which are incorporated herein by reference.

Applicants respectfully submit that all of the claims are allowable based on the analysis of *Graham* factors as well.

The *Graham* factual inquiries, which establish a guide for determining obviousness, are: (1) determining the scope and contents of the prior art; (2) ascertaining the differences between the prior art and the claims at issue; (3) resolving the level of ordinary skill in the pertinent art; and (4) evaluating any evidence of secondary considerations. (*See KSR,* 127 S.Ct. 1727, 1729-30 (*citing Graham,* 383 U.S. at 15-7)).

Under the guideline set forth in *Graham*, claim 41 is unobvious over Young in view of Luscombe for at least the following reasons:

1) The scope and contents of Young and Luscombe in comparison with claim 41

The *Graham* factual inquiries require one to determine the scope and contents of the prior art and ascertain the differences between the prior art and the claim(s) at issue. In this regard, Young discloses the methods and compositions of using optical isomers of sibutramine in the treatment of certain disorders. Luscombe discloses racemic sibutramine and its metabolites as monoamine reuptake inhibitors.

In contrast, claim 41 recites the use of optically pure didesmethylsibutramine in the treatment of depression. Therefore, Young and Luscombe, even if they were combined, are completely silent regarding the subject matter recited by claim 41 because there is no disclosure of optically pure didesmethylsibutramine in either Young or Luscombe.[2] Thus, the issue is whether those skilled in the art, having been made aware of Young and Luscombe's disclosures, would have found the use of optically pure didesmethylsibutramine for the treatment of depression, as recited by claim 41, obvious. Applicants respectfully submit that they would not have arrived at claim 41 given the teachings of Young and Luscombe for at least the following reasons.

[2] In this regard, the issue here is not even whether combining the disclosures of these references would have been obvious because the references, even when combined, do not disclose or implicate the claimed invention. Applicants respectfully submit that the rejection should be withdrawn for this reason alone.

2) Those skilled in the art would not have arrived at claim 41 given the teachings of Young and Luscombe

As the Examiner recognizes, Young discloses the use of optical isomers of the parent drug sibutramine. It appears that the Examiner alleges that this disclosure, combined with Luscombe's disclosure regarding racemic didesmethylsibutramine, somehow would have led those skilled in the art to the claimed method. However, the use of a parent compound is different from the use of its metabolites, *i.e.*, the pharmacological properties of a parent compound do not necessarily predict or suggest those of its metabolites. (*See, e.g., In re Grabiak*, 769 F.2d 729, 731 (Fed. Cir. 1985) ("Generalization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from another.")). Therefore, regardless of what has been disclosed in Young with regard to the optical isomers of sibutramine, such disclosure has no specific bearing on the patentability of the claims directed to the use of optical isomers of didesmethylsibutramine. In other words, a person of ordinary skill in the art would not have been prompted to use the optical isomers of didesmethylsibutramine based on Young's disclosure of the use of optical isomers of sibutramine.

Further, contrary to the Examiner's assertion, Luscombe does not teach that didesmethylsibutramine is considerably more active than sibutramine. According to Table 1 of Luscombe on page 131, desmethylsibutramine, didesmethylsibutramine and sibutramine all show similar *in vivo* activities in the Porsolt test and in the assay of preventing tetrabenazine-induced ptosis. In fact, Luscombe shows that didesmethylsibutramine may be somewhat less potent than sibutramine in reversing reserpine-induced hypothermia and preventing reserpine-induced ptosis. This is evidenced by the fact that didesmethylsibutramine demonstrated a higher ED_{50} in these tests than sibutramine. (*See* Luscombe, Table 1 on page 131). Moreover, the disclosure that didesmethylsibutramine is reportedly more potent than the parent compound *in vitro* cannot weigh against the patentability of the claimed methods on the face of the disclosure in the same reference that didesmethylsibutramine exhibits a potency similar to sibutramine *in vivo*. (*See* Luscombe, Tables 1-3 and Figures 2 and 3 for the *in vivo* data in comparison with the *in vitro* data in Table 3). The *in vivo*, not the *in vitro*, activity is what determines whether an agent should be "administered to a patient," as recited by claim 41. Accordingly, those of ordinary skill in the art reading Luscombe would not have been prompted to use didesmethylsibutramine, much less

an optically pure didesmethylsibutramine, in view of Luscombe's disclosure that no improved pharmacological activity *in vivo* is observed for didesmethylsibutramine.

Finally, as claims 42-50 depend from claim 41, these claims are unobvious over Young and Luscombe for at least the same reasons. Therefore, Applicants respectfully request that the rejection of claims under 35 U.S.C. § 103 be withdrawn.

B. The Rejection Under 35 U.S.C. § 102(b) Should Be Withdrawn

On page 6 of the Office Action, claims 41 is rejected as allegedly anticipated by Scott *et al.*, *Br. J. Pharmacol.*, 111: 97-102 (1994) ("Scott"). Applicants respectfully traverse.

As well-established, "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." (*Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987)). Scott discloses the effects of [didesmethylsibutramine] on the responses evoked by visual stimulation and ionophoretic application of noradrenaline, 5-hydroxytryptamine and excitatory amino acids in the rat dorsolateral geniculate nucleus ("dLGN"). In this reference, didesmethylsibutramine and/or other drugs were directly applied onto the dLGN in rats under anesthesia; the activities of the neurons were then recorded. Scott, however, does not teach the use of optically pure didesmethylsibutramine or disclose administering didesmethylsibutramine to a patient to treat depression. Therefore, Scott fails to disclose "each and every element" in claim 41. Applicants respectfully submit that claim 41 is not anticipated by Scott, and thus, respectfully request that the rejection be withdrawn.

Conclusion

For at least the foregoing reasons, Applicants respectfully submit that all of the pending claims are allowable, and request that the rejection of the claims be withdrawn.

No fee is believed due for the submission of this paper. If any fees are required, however, for the submission of this paper, or to avoid abandonment of this application, please charge such fees to Jones Day Deposit Account No. 503013.

Respectfully submitted,

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